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CLINICAL REVIEW

Sleep–wake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis

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SUMMARY

Over the past decade, researchers have shifted focus from the manic and depressive episodes to the interepisode period in the study of sleep–wake disturbance in bipolar disorder. The objective of this systematic review was to compile and synthesize studies that employed sleep diary, actigraphy, polysomnography, and questionnaires to compare sleep–wake patterns in people with interepisode bipolar disorder or high-risk individuals vs. normal controls and/or people with primary insomnia. We searched key databases until June 2013. Our search identified 21 eligible studies, yielding 24 sleep–wake variables. A total of 531 people with interepisode bipolar disorder, 157 high-risk individuals, 678 normal controls and 67 adults with primary insomnia were evaluated. Using a random-effects model, our analyses suggest that adults with interepisode bipolar disorder appear worse than normal controls in most variables and comparable to adults with primary insomnia in certain aspects. Sleep onset latency, wake after sleep onset, and variability of sleep–wake variables were most consistently impaired in interepisode bipolar disorder. In comparison with controls, high-risk individuals were found to have higher variability in sleep efficiency and lower relative amplitude. The findings provide a foundation for the search for candidate endophenotypes and the development of novel interventions for bipolar disorder.

Introduction

Sleep–wake disturbance has been considered a cardinal feature of the manic and depressive episodes of bipolar disorder for decades. It was not until the past few years that researchers shifted focus to the interepisode period. Several cross-sectional and longitudinal studies have shown that adults with interepisode bipolar disorder who suffer from sleep–wake disturbance have more unfavorable course of illness and outcomes. For example, Giglio et al. [1] noted that bipolar disorder patients with sleep disturbance, although euthymic, exhibited worse functioning and quality of life compared with those without sleep disturbance. Gruber et al. [2] reported that shorter sleep duration was associated with greater severity of manic symptoms at baseline and across 12 mo, while higher sleep variability was associated with greater severity of both manic and depressive symptoms at baseline and across 12 mo in an interepisode sample. Sylvia et al. [3] found that baseline sleep disturbance was associated with a history of psychosis, suicidal attempts and an elevated risk of mood episode recurrence at follow-up among euthymic patients with bipolar disorder.

Studies have found that sleep–wake disturbance is prevalent during the interepisode period of bipolar disorder. A recent narrative review reported that 15–100% of euthymic individuals diagnosed with bipolar disorder experience difficulty initiating and maintaining sleep as well as early morning awakening [4]. Besides insomnia symptoms, other sleep–wake disturbances, such as irregular sleep–wake patterns and excessive daytime sleepiness, are also common [4]. Although there is a growing literature indicating that sleep–wake disturbance is prevalent in the interepisode period, findings are still inconclusive. For example, some studies found that people with interepisode bipolar disorder had longer sleep duration according to actigraphy relative to controls [5–8], while other studies did not detect any significant differences [9–12]. One reason behind the discrepancies is that most studies have small sample size so the analyses may have been underpowered. Differences in inclusion criteria, demographic characteristics and medication use might also contribute to the variation in study results.

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Abbreviations

ADHD	attention-deficit and hyperactivity disorder
CBT-I	cognitive behavioral therapy for insomnia
ESS	Epworth sleepiness scale
ISI	insomnia severity index
NWAK	number of awakenings
PSQI	Pittsburgh sleep quality index
REM	rapid-eye movement
SE	sleep efficiency
SOL	sleep onset latency
SWS	slow–wave sleep
TIB	time in bed
TST	total sleep time
WASO	wake after sleep onset

Previous studies have also found sleep–wake disturbance in people at risk for developing bipolar disorder. For instance, high-risk individuals, defined by the Hypomanic Personality Scale [13], have been found to exhibit more variable sleep duration than matched controls on both subjective and objective sleep measures [14,15]. Such findings lend support to the hypothesis that sleep and circadian rhythm disturbances may be candidate endophenotypes for bipolar disorder [16–20].

Although several narrative reviews on sleep–wake disturbance in bipolar disorder have been published over the past few years [4,20–22], no systematic review and meta-analysis has been conducted. This study aimed to compile previous studies on sleep–wake disturbance in interepisode bipolar disorder and high-risk individuals systematically and summarize their results quantitatively. We compared sleep–wake variables of people diagnosed with interepisode bipolar disorder or at risk for bipolar disorder with people with primary insomnia and/or healthy controls.

Method

Search and selection of studies

We conducted a systematic review and meta-analysis in accordance with a predetermined protocol. We searched the MEDLINE, Embase, PsycINFO and ProQuest Dissertations and Theses A&I databases from inception to June 2013 using the grouped terms (bipolar* OR mania OR manic* OR euthymic*) and (sleep* OR hypersomnia* OR insomnia* OR wakeful*). To enhance search sensitivity, the reference lists of the retrieved articles and review papers were further checked to identify potentially relevant articles.

Two authors (THN and FYH) searched the databases and selected the relevant publications independently. First, we examined the titles to exclude articles obviously impertinent to the current systematic review. Then, we reviewed the abstracts of potentially relevant articles and excluded articles not fulfilling the inclusion criteria. Finally, we assessed the full-text of the remaining articles to determine eligibility for inclusion in the systematic review. Disagreements regarding eligibility were resolved by discussion. We contacted authors to obtain unreported data relevant to the current systematic review, according to a recent guideline on meta-analysis of observational studies [23].

Inclusion criteria

Articles eligible for inclusion were published patient-control studies that examined sleep–wake disturbance in people diagnosed with interepisode bipolar disorder, in comparison with healthy controls or people diagnosed with primary insomnia and studies that examined the same topic in people at risk of bipolar disorder, defined by familial history and questionnaire scores, in comparison with controls. Using actigraphy, sleep diary or polysomnography, the included studies measured at least one of the following sleep–wake variables: bedtime, rise time, time in bed (TIB), total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO), number of awakenings (NWAK), sleep efficiency (SE), variability in TST, SOL, WASO and SE, interdaily stability, intradaily variability and relative amplitude of the rest-activity cycle, acrophase, % stage 1, 2, slow-wave sleep (SWS) and rapid-eye movement (REM) sleep, REM latency and duration of the first REM period. Other than the above variables, studies were also included if they assessed sleep using the following sleep questionnaires: the Pittsburgh sleep quality index (PSQI), insomnia severity index (ISI) and Epworth sleepiness scale (ESS). These variables were chosen as they have been commonly examined in the literature on sleep–wake disturbance in interepisode bipolar disorder. Studies were excluded if participants were in a mood episode or data amenable to meta-analysis were not presented and not provided by authors upon request. When several studies used the same data set and assessed the same sleep–wake variable, we only included the study with the largest number of participants for the variable to avoid double-counting.

Data extraction

One author (THN) extracted data and the other (FHH) checked the accuracy of the extracted data. The following information was extracted: number of participants, age, gender, recruitment source, inclusion/exclusion criteria, concurrent medications and sleep–wake variables.

Data analysis

All statistical analyses were performed with the RevMan 5.2 for Windows (Cochrane Collaboration, Oxford, UK; see http://ims.cochrane.org/revman). We calculated the standardized mean difference (95% CI) in sleep–wake variables between the bipolar and control groups. Due to differences in demographic characteristics and inclusion/exclusion criteria, we expected the studies would be heterogeneous a priori and sleep–wake disturbances would vary more than expected by chance alone. Therefore, we employed the random-effects model [24] and the inverse-variance method to calculate summary estimates. Variables assessed in only one study were not meta-analyzed and were reviewed narratively. We computed the I^2 statistic to evaluate the heterogeneity between studies. As suggested by Higgins et al. [25], I^2 values of 0%, 25%, 50% and 75% indicate no, low, moderate and high heterogeneity. We also employed the χ^2-test, with P-value less than 0.10 indicating significant heterogeneity.

Results

Search results and included studies

The searches yielded 5703 citations, of which 1751 were duplicates. We discarded 3783 articles due to irrelevance at title review, yielding 169 articles for abstract review and 52 for full-text review. 31 of the 52 studies were excluded due to various reasons. 21 remaining articles were included in the current systematic review and meta-analysis (Fig. 1).

The study design of the included studies is summarized in Table 1. Among the 21 articles, 14 (66.7%) were on adults with interepisode bipolar disorder, four on high-risk individuals, two on

children and adolescents with interepisode bipolar disorder, and one on both adults with interepisode bipolar disorder and high-risk individuals. Sample size ranged from 20 to 209, with a total of 1433. Studies were conducted in the United States ($n = 8$), United Kingdom ($n = 5$), Canada ($n = 2$), Brazil ($n = 2$), Germany ($n = 2$), Australia ($n = 1$) and Italy ($n = 1$). Sleep–wake disturbance was assessed by actigraphy ($n = 13$), diary ($n = 12$), polysomnography ($n = 5$), and self-report questionnaires ($n = 7$). Most of the participants with interepisode bipolar disorder were on psychotropic medications. Table 2 shows the key results of all included studies.

Comparison between adult bipolar and healthy control participants

Actigraphy

Compared with healthy controls, adults with interepisode bipolar disorder had significantly longer TST (SMD = 0.65, 95% CI 0.30 to 1.00, $I^2 = 63\%$), SOL (SMD = 0.37, 95% CI 0.16 to 0.59, $I^2 = 9\%$), WASO (SMD = 0.26, 95% CI 0.07 to 0.46, $I^2 = 0\%$) and TIB (SMD = 0.87, 95% CI 0.26 to 1.48, $I^2 = 60\%$). Among adults with interepisode bipolar disorder, there was greater variability in TST (SMD = 0.48, 95% CI 0.14 to 0.81, $I^2 = 0\%$), SOL (SMD = 0.51, 95% CI 0.18 to 0.84, $I^2 = 0\%$) and WASO (SMD = 0.48, 95% CI 0.15 to 0.81, $I^2 = 0\%$). In addition, they had lower activity counts (SMD = −1.07, 95% CI −1.68 to −0.45, $I^2 = 68\%$) and earlier acrophase (SMD = −2.81, 95% CI −4.61 to −1.00, $I^2 = 90\%$). There was no significant between-group difference in NWAK (SMD = −0.12, 95% CI −0.48 to 0.23, $I^2 = 0\%$), SE (SMD = −0.03, 95% CI −0.30 to 0.24, $I^2 = 37\%$) and variability in SE (SMD = 0.22, 95% CI −0.12 to 0.56, $I^2 = 6\%$) (Fig. 2). Jones et al. [9] reported significantly greater intradaily variability, lower interdaily stability and no difference in relative amplitude of the rest-activity pattern among patients with interepisode bipolar disorder relative to controls.

Sleep diary

Compared with healthy controls, adults with interepisode bipolar disorder had significantly lower SE (SMD = −0.77, 95% CI −1.16 to −0.39, $I^2 = 52\%$), longer SOL (SMD = 0.86, 95% CI 0.45 to 1.26, $I^2 = 56\%$), WASO (SMD = 0.51, 95% CI 0.23 to 0.80, $I^2 = 21\%$) and TIB (SMD = 0.47, 95% CI 0.16 to 0.77, $I^2 = 0\%$) and greater NWAK (SMD = 0.65, 95% CI 0.27 to 1.03, $I^2 = 55\%$) and variability in TST (SMD = 0.42, 95% CI −0.01 to 0.84, $I^2 = 13\%$), SOL (SMD = 0.49, 95% CI 0.10 to 0.88, $I^2 = 0\%$), WASO (SMD = 0.64, 95% CI 0.24 to 1.03, $I^2 = 0\%$) and SE (SMD = 0.72, 95% CI 0.32 to 1.12, $I^2 = 0\%$). There was no significant between-group difference in TST (SMD = 0.08, 95% CI −0.23 to 0.38, $I^2 = 32\%$), bedtime (SMD = −0.09, 95% CI −0.40 to 0.21, $I^2 = 0\%$) and rise time (SMD = 0.61, 95% CI −0.24 to 1.47, $I^2 = 91\%$) (online Fig. S1).

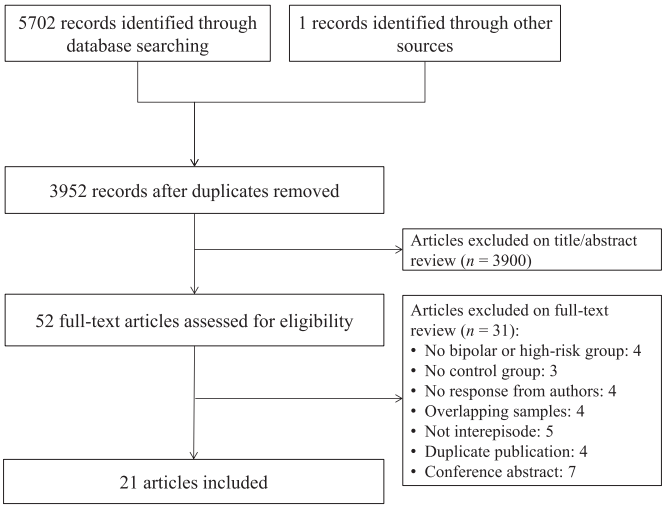


Fig. 1. Selection of studies.

Polysomnography

Compared with healthy controls, adults with interepisode bipolar disorder had significantly higher % stage 1 (SMD = 0.55, 95% CI 0.05 to 1.05, $I^2 = 0\%$). There was no between-group difference in TST (SMD = 0.28, 95% CI −0.11 to 0.67, $I^2 = 0\%$), SOL (SMD = 0.18, 95% CI −0.21 to 0.57, $I^2 = 0\%$), WASO (SMD = 0.08, 95% CI −0.31 to 0.46, $I^2 = 0\%$), SE (SMD = −0.10, 95% CI −0.49 to 0.28, $I^2 = 0\%$), % stage 2 (SMD = −0.30, 95% CI −1.32 to 0.72, $I^2 = 71\%$), % SWS (SMD = −0.22, 95% CI −0.68 to 0.24, $I^2 = 0\%$), % REM sleep (SMD = 0.58, 95% CI −0.21 to 1.36, $I^2 = 69\%$), REM latency (SMD = −0.12, 95% CI −0.53 to 0.29, $I^2 = 0\%$) and duration of the first REM period (SMD = 0.37, 95% CI −0.09 to 0.83, $I^2 = 0\%$) (Fig. S2). Kaplan et al. [26] reported no significant between-group differences in NWAK. Eidelman et al. [27] reported no significant differences in REM density. Sitaram et al. [28] reported no significant differences in REM density of the first, second, third REM periods and of the overall period, duration of the second and third REM periods, and number of REM periods. Knowles et al. [29] reported no significant differences in % stage 3 and 4 and REM profusion.

Questionnaire

Compared with healthy controls, adults with interepisode bipolar disorder had significantly higher scores on PSQI (SMD = 1.55, 95% CI 1.27 to 1.82, $I^2 = 0\%$), ISI (SMD = 1.28, 95% CI 0.83 to 1.72, $I^2 = 0\%$) and ESS (SMD = 0.50, 95% CI 0.20 to 0.79, $I^2 = 1\%$) (Fig. 3).

Comparison between adult bipolar and primary insomnia participants

Actigraphy

Compared with adults with insomnia, adults with interepisode bipolar disorder had significantly longer TST (SMD = 0.87, 95% CI 0.07 to 1.67, $I^2 = 53\%$) and lower activity counts (SMD = −0.77, 95% CI −1.30 to −0.23, $I^2 = 0\%$). There was no significant between-group difference in SOL (SMD = −0.35, 95% CI −1.02 to 0.33, $I^2 = 39\%$) and WASO (SMD = 0.09, 95% CI −0.51 to 0.68, $I^2 = 23\%$) (Fig. S3). St-Amand et al. [12] reported no significant between-group difference in SE.

Sleep diary

Compared with adults with insomnia, adults with interepisode bipolar disorder had significantly longer TST (SMD = 0.64, 95% CI 0.16 to 1.12, $I^2 = 41\%$), higher SE (SMD = 0.57, 95% CI 0.18 to 0.96, $I^2 = 18\%$) and lower WASO (SMD = −0.76, 95% CI −1.45 to −0.06, $I^2 = 70\%$), but no significant difference in SOL (SMD = −0.52, 95% CI −1.50 to 0.46, $I^2 = 85\%$) (Fig. S4). Talbot et al. [30] reported no significant between-group difference in NWAK, bedtime, rise time and TIB.

Questionnaire

Harvey et al. [5] reported that adults with interepisode bipolar disorder had significantly lower scores on PSQI than adults with primary insomnia. St-Amand et al. [12] reported adults with interepisode bipolar disorder had significantly lower ISI scores than adults with primary insomnia but no between-group difference in ESS scores.

Comparison between children and adolescent bipolar and healthy control participants

Mehl et al. [31] found that children with bipolar disorder, identified by the Child Behavior Checklist, had lower

Table 1
Summary of study design.

Study	Participants	Age, y Mean (SD)/% female	Recruitment source	Inclusion/exclusion criteria	Sleep measures (period)	Concurrent psychotropic medications
Ankers and Jones, 2009 [14]	31 HR	20.9 (3.7)/74.2%	University	HPS ≥ 9th decile. Absence of current mood episode and history of bipolar spectrum disorders, psychosis or insomnia (SCID/NP).	Actigraphy and sleep diary (one week)	HR: 3.2% on antidepressants HC: Nil
	24 HC	22.1 (2.8)/66.7%		HPS ≤ mean + SD/2. Absence of current mood episode and history of bipolar spectrum disorders, psychosis, insomnia or subsyndromal hypomania.		
Bullock and Murray, 2013 [65]	36 HR	22.3 (2.9)/69%	University	GBI ≥ 9th decile and age 18–30 y. Absence of current mood episode and history of manic/mixed or hypomanic episode, shift work and physical conditions that might affect locomotor activity measurement.	Actigraphy (one week)	HR & HC: NR
	36 HC	21.0 (2.3)/75%		GBI ≤ 1st decile and age 18–30 y. Absence of current mood episode and history of manic/mixed or hypomanic episode, shift work and physical conditions that might affect locomotor activity measurement.		
Eidelman et al., 2010 [27]	19 BD I 03 BD II	40.0 (10.1)/90.9%	Community	DSM-IV criteria for BD I or II without current mood episode in previous month (SCID); IDS-C ≤ 11, YMRS ≤ 7, under psychiatric care and stable living condition. Absence of sleep disorder (DSISD, RDI < 5, PLMI < 15), current alcohol or substance abuse (SCID) and history of severe medical disease.	In-lab PSG (1 night)	BD: 95.5% HC: Nil
	22 HC	40.0 (12.6)/77.3%		Absence of subjective sleep complaints and sleep disorder (DSISD, RDI < 5, PLMI < 15), current or past Axis I psychiatric disorder (SCID), first-degree relatives with BD or schizophrenia and history of head injury or severe medical disease.		
Eidelman et al., 2012 [66]	35 BD I 0	34.7 (10)/57.1%	Community	DSM-IV criteria for BD I without current mood episode in previous month (SCID); IDS-C ≤ 23, YMRS ≤ 11, under psychiatric care and stable living condition. Absence of sleep disorder (DSISD), alcohol or substance abuse/dependence in previous six months (SCID) and history of head injury or severe progressive medical disease.	Actigraphy and sleep diary (four weeks) and DSISD	BD: 74.3% Antidepressants: 40.0% Antipsychotics: 57.1% Mood stabilizers: 25.7% HC: NR
	38 HC	32.9 (12.9)/51.3%		Stable living condition. Absence of subjective sleep complaints, sleep disorder (DSISD), current or past Axis I psychiatric disorder (SCID) and history of head injury or severe progressive medical disease.		
Gershon et al., 2012 [10]	32 BD I	34.7 (10.5)/62.5%	Community	DSM-IV criteria for BD I without current mood episode in previous month (SCID); IDS-C ≤ 23, YMRS ≤ 11, under psychiatric care and stable living condition. Absence of sleep disorder (DSISD), alcohol or substance abuse/dependence in previous six months (SCID) and medical condition that interferes with sleep.	Actigraphy and sleep diary (eight weeks), PSQI, ISI and DSISD	BD: 93.8% Monotherapy: 40.6% Antidepressants: 50.0% Hypnotics: 20.0% Lamotrigine: 43.3% Lithium: 16.7% Valproic acid: 10.0% HC: Nil
	36 HC	33.3 (12.6)/52.8%		IDS-C ≤ 23, YMRS ≤ 11, ISI ≤ 7, PSQI ≤ 5 and stable living condition. Absence of sleep disorder (DSISD), current or past Axis I psychiatric disorder (SCID) and medical condition that interferes with sleep.		
Harvey et al., 2005 [5]	20 BD I	39.6 (15.2)/50%	Tertiary setting and community	DSM-IV criteria for BD I (SCID). Interepisode status confirmed using HAM-D and YMRS.	Actigraphy and sleep diary (eight days and nights), DBAS, PSQI, SDQ and semi-structured interview	BD: 100% Benzodiazepine receptor agonists: 40% OTC sleep aids: 10% Others including carbamazepine, fluoxetine, lamotrigine, lithium,
	20 HC	36.9 (11.6)/65%		Absence of sleep difficulties and hypnotic use in previous month (IDI).		
	20 INS	29.8 (9.9)/55%		DSM-IV criteria for primary insomnia (IDI).		

(*continued on next page*)

Table 1 (*continued*)

Study	Participants	Age, y Mean (SD)/% female	Recruitment source	Inclusion/exclusion criteria	Sleep measures (period)	Concurrent psychotropic medications
						valproic acid and venlafaxine HC: Nil INS: 30% on medications OTC sleep aids: 20% Sedative antidepressants: 10%
Jones et al., 2005 [9]	19 BD I	44.4 (13.1)/73.7%	Tertiary setting and community	DSM-IV criteria for BD I without current mood episode (SCID). Asymptomatic or low level of subsyndromal symptoms according to HAM-D and MAS. Absence of schizoaffective disorder and current primary alcohol or substance problem (SCID).	Actigraphy and sleep diary (one week)	BD: 100% Lithium: 89.5% Valproic acid: 31.6% HC: NR
	19 HC	46.9 (14.8)/73.7%		Absence of current or past Axis I psychiatric disorder (SCID).		
Jones et al., 2006 [33]	25 HR	16.2 (2.0)/76%	Tertiary setting and community	Children of parents who meet DSM-IV criteria for BD I without current mood episode (SCID).	Actigraphy and sleep diary (one week) and PSQI	HR & HC: Nil
	22 HC	16.86 (1.9)/72.7%		Children of parents without current or past mental health problems (SCID).		
Kaplan et al., 2012 [26]	23 BD I 4 BD II	33.1 (10.3)/85.2%	Tertiary setting and community	DSM-IV criteria for BD I or II (SCID), IDS-C $\leq$ 11, YMRS $\leq$ 7 and under psychiatric care. Absence of suicidal risk, major sleep disorder (DSISD or PSG), current alcohol or substance abuse/dependence (SCID/NP), severe medical condition and brain injury.	Actigraphy, sleep diary and in-lab PSG (average of two nights) and DSISD	BD: 96.3% Monotherapy: 11.1% Antidepressants: 81.5% Antipsychotics: 48.1% Anxiolytics: 22.2% Hypnotics: 3.7% Mood stabilizers: 70.4%
	27 HC	38.1 (13.0)/70.4%		IDS-C $\leq$ 11 and YMRS $\leq$ 7. Absence of current or past Axis I psychiatric disorder (SCID), major sleep disorder (DSISD or PSG), severe medical condition and brain injury.		HC: Nil
Knowles et al., 1986 [29]	10 BD I	35.5 (NR)/30.0%	Tertiary setting and community	BD or family history of BD. Absence of sleep apnea, current mood episode and mood symptoms in the 21 days after sleep assessment.	In-lab PSG (average of five nights)	BD: discontinued for at least three weeks. HC: NR
	10 HC	NR		Absence of past or family history of affective illness.		
Mehl et al., 2006 [31]	13 BD 13 HC	6.7 (0.7)/46.2% 6.6 (0.6)/46.2%	Community	BD per the Child Behavior Checklist. Matched to the BD group for gender, age, ethnicity, parental-report ADHD severity, psychotropic medication usage and apnea-hypopnea index.	Sleep questionnaire and in-lab PSG (1 nights)	BD: 23.0% Antihypertensive: 15.4% Atypical antipsychotics: 7.7% Psychostimulants: 15.4% HC: 23.0% Antihypertensives 7.7% Atypical antipsychotics: 7.7% Psychostimulants 15.4%
Meyer and Maier, 2006 [15]	56 HR	18 (2.2)/69.6%	High school, college, or vocational school	HPS $\geq$ 9th decile, infrequency scores $\leq$ 2 and EPI-L $\leq$ 4. Native German.	Sleep diary (28 days)	NR
	48 HC	18.3 (2.1)/70.8%		HPS and MPT-R $\leq$ mean $\pm$ 1/2 SD, infrequency scores $\leq$ 2 and EPI-L $\leq$ 4. Native German.		
Millar et al., 2004 [11]	19 BD I	47.3 (10.6)/57.9%	Tertiary setting and community	DSM-IV criteria for BD I without current mood episode. Absence of shift work, comorbid psychiatric disorder and treatment for alcohol or substance problems.	Actigraphy and sleep diary (average of four nights)	BD: 94.7% Antidepressants: 57.9% Antipsychotics: 52.6% Hypnotics: 10.5% Mood stabilizers: 78.9%
	19 HC	45.8 (10.9)/57.9%		Absence of shift work and current or lifetime major psychiatric disorder (SCID).		HC: NR
Mullin et al., 2011 [32]	5 BD I 4 BD II 4 BD-NOS	14.4 (2.1)/53.8%	Tertiary setting and community	DSM-IV-TR criteria for BD I, II, or NOS without current mood episode (K-SADS-PL) and parental-report YMRS < 27. Absence of current or past sleep disorder, schizophrenia, mental retardation or autistic spectrum disorder.	Actigraphy and sleep diary (four nights)	BD: 100% Anticonvulsants/mood stabilizers: 84.6% Antidepressants: 46.2% Atomoxetine: 7.7% Atypical antipsychotics: 76.9%
	21 HC	14.1 (2.0)/47.6%		Absence of psychological problems.		Clonazepam: 7.7%
	14 ADHD-C	15.1 (2.1)/21.4%		DSM-IV-TR criteria for ADHD-C (K-SADS-PL). Absence of current or past sleep disorder, schizophrenia, mental		HC: Nil ADHD: Overall % NR Antidepressants: 21.4%

Table 1 (*continued*)

Study	Participants	Age, y Mean (SD)/% female	Recruitment source	Inclusion/exclusion criteria	Sleep measures (period)	Concurrent psychotropic medications
				retardation or autistic spectrum disorder.		Atomoxetine: 7.1% Psychostimulants: 50%
Ritter et al., 2012 [7]	22 BD I or II	32.7 (10.0)/40.9%	Tertiary setting and community	DSM-IV criteria for BD I or II (SCID), HAMD-17 $\leq$ 15, YMRS $\leq$ 10 and age $\geq$ 16 y. Absence of sleep disorder, substance abuse, psychotic disorder, organic brain disorder, borderline personality disorder, PTSD and other psychiatric disorder that would severely affect compliance with study protocol (SCID) and medical condition that interferes with sleep. Sedative medications only allowed for participants who had taken them at a stable dosage for at least one month.	Actigraphy (six nights) and BIPS-Q	BD: 100% Antidepressants: 18.2% Aripiprazole: 4.5% Carbamazepine: 9.1% Clozapine: 4.5% Lamotrigine: 13.6% Lithium: 63.6% Olanzapine: 4.5% Quetiapine: 40.9% Valproic acid: 36.4%
	28 HC	28.3 (7.2)/42.9		HAMD-17 $\leq$ 15, YMRS $\leq$ 10 and age $\geq$ 16 y. Absence of current or past psychiatric disorder except for remitted adjustment disorder (SCID), first-degree relative with psychiatric disorder except for dementia and adjustment disorder, psychotropic medication use in the past four weeks, sleep disorder and medical condition that interferes with sleep.		HC: Nil, except for antihistamines used to treat allergy.
	9 HR	25.4 (3.6)/22.2%		HAMD-17 $\leq$ 15, YMRS $\leq$ 10, age $\geq$ 16 y and either having subthreshold mood symptoms and a first or second degree relative with BD, major depression, or schizoaffective disorder or past major depressive episode with subthreshold manic symptoms. Absence of sleep disorder, substance abuse, psychotic disorder, organic brain disorder, borderline personality disorder, PTSD, other psychiatric disorder that would severely affect compliance with study protocol (SCID) and medical condition that interferes with sleep.		HR: 11.1% Bupropion: 100%
Rocha et al., 2013 [67]	94 BD I 11 BD II	47.0 (18.5)/77.1%	Tertiary setting	DSM-IV-TR criteria for BD without current mood episode (MINI-plus), HAM-D and YMRS < 7, alcohol dependence and functional recovery.	PSQI	BD: 100% Lithium: 47.6% Anticonvulsants: 74.3% Atypical: 34.3% Typical: 33.3% Benzodiazepines: 61% Antidepressant: 32.4% Stimulants: 0%
	104 HC	46.0 (36.0)/73.1%		Absence of current or past Axis I psychiatric disorder (MINI-plus), alcohol dependence and current use of psychiatric medications.		HC: Nil
Salvatore et al., 2008 [8]	36 BD I	44.4 (9.8)/80.6%	Tertiary setting and community	DSM-IV criteria for BD I without current mood episode for at least eight weeks (SCID), HAM-D < 10, YMRS < 14 and functional recovery.	Actigraphy (three days and nights)	BD: 100% Monotherapy: 23.3% Anticonvulsants: 77.8% Antidepressants: 52.8% Antipsychotics: 75.0% Hypnotics: 77.8% Lithium 72.2%
	32 HC	42.3 (10.8)/75.0%		Absence of Axis I psychiatric disorder (SCID) and major medical condition.		HC: NR
Sitaram et al., 1982 [28]	14 BD	30.0 (6.1)/57.1%	NR	RDC criteria for BD without current mood episode for at least three months and functional recovery.	In-lab PSG (1 night or average of two nights)	BD: psychotropic medications discontinued for at least two weeks before study.
	15 HC	26.8 (4.4)/46.7%		Absence of medical condition, past psychiatric disorder (SADS) and relatives with affective illness.		HC: NR
St-Amand et al., 2009 [12]	11 BD I 03 BD II	44.6 (11.0)/50%	Tertiary setting and community	DSM-IV criteria for BD I or II (SCID), BDI-II $\leq$ 19, HAM-D $\leq$ 13 and stable medication dosage for three months before and during study. Absence of rapid-cycling, alcohol or substance dependence, shift work, unstable work schedule and medical condition that interferes with sleep.	Actigraphy and sleep diary (two weeks), ESS and ISI	BD: 100% Anticonvulsants: 71.4% Antidepressants: 64.3% Antipsychotic: > 50% Lithium: 42.9% Hypnotics: 42.9%
	13 HC	47.2 (10.4)/46.2%		Absence of Axis I psychiatric disorder or insomnia (SCID and IIS), shift work, unstable work schedule and medical condition that interferes with sleep.		HC: Nil

(*continued on next page*)

Table 1 (*continued*)

Study	Participants	Age, y Mean (SD)/% female	Recruitment source	Inclusion/exclusion criteria	Sleep measures (period)	Concurrent psychotropic medications
	13 INS	42.8 (15.9/61.5%		DSM-IV-TR and ICSD-R criteria for insomnia. Absence of shift work, unstable work schedule, medical condition that interferes with sleep and hypnotic use more than two nights per week.		INS: 38.5% OTC sleep aids: 23.1% Temazepam: 7.7% Zopiclone: 7.7%
Talbot et al., 2012 [30]	43 BD I 06 BD II	36.8 (11.8)/69.4%	Tertiary setting and community	DSM-IV-TR criteria for BD I or II (SCID), IDS-C < 12, YMRS < 8 and under psychiatric care. Absence of narcolepsy, sleep apnea and PLMD (DSISD) and current alcohol or substance abuse/ dependence (SCID).	Sleep diary (7 nights) and DSISD	BD: 93.9% Antidepressants: 71% Antipsychotics: 71% Anxiolytics: 57% Mood stabilizers: 76% Prescription sleep aids: 2%
	52 HC	36.9 (11.6)/67.3%		IDS-C < 12 and YMRS < 8. Absence of current or past Axis I psychiatric disorder (SCID) and sleep disorder (DSISD).		HC: Nil INS: 5.9% Antidepressants: 2.9% Prescription sleep aids: 2.9%
	34 INS	29.8 (9.9)/76.5%		Primary insomnia as primary diagnosis (DSISD), IDS-C < 12 and YMRS < 8. Absence of narcolepsy, sleep apnea and PLMD (DSISD) and current depression and alcohol or substance abuse/ dependence (SCID).		
Walz et al., 2012 [68]	81 BD I, II or NOS	43.5 (12.3)/71.6%	Tertiary setting	DSM-IV criteria for BD I, II or NOS without current mood episode (SCID). Asymptomatic or low level of subsyndromal symptoms according to HAM-D and YMRS. Absence of mental retardation.	ESS, PSQI	NR
	79 HC	45.8 (12.7)/73.8%		Absence of current Axis I psychiatric disorder (SCID) and first-degree relatives with BD, schizophrenia or other psychiatric disorder.		

ADHD, attention-deficit and hyperactivity disorder; ADHD-C, ADHD-combined type; BD, bipolar disorder; BDI-II, Beck depression inventory, second edition; BIPS-Q, bipolar sleep questionnaire; DBAS, dysfunctional beliefs and attitudes about sleep scale; DSISD, Duke structured interview for sleep disorder; EPI-L, Eysenck personality inventory – lie scale; ESS, Epworth sleepiness scale; GBI, general behavior inventory; HAM-D, Hamilton rating scale for depression; HAMD-17, 17-item Hamilton rating scale for depression; HC, healthy control; HPS, hypomanic personality scale; HR, high-risk individuals; ICSD-R, international classification of sleep disorders, revised; IDI, insomnia diagnostic interview; IDS-C, clinician-rated inventory of depressive symptomatology; IIS, insomnia interview schedule; INS, primary insomnia; ISI, insomnia severity index; K-SADS-PL, kiddie-schedule for affective disorders and schizophrenia – present and lifetime version; MAS, Bech mania scale; MINI, mini international neuropsychiatric interview; MPT-R, Munich personality test – rigidity subscale; NOS, not otherwise specified; NR, not reported; OTC, over-the-counter; PLMD, periodic limb movement disorder; PLMI, periodic limb movement index; PSG, polysomnography; PSQI, Pittsburgh sleep quality index; PTSD, posttraumatic stress disorder; RDC, research diagnostic criteria; RDI, respiratory distress index; SADS, schedule for affective disorders and schizophrenia; SCID, structured clinical interview for DSM-IV; SCID/NP, structured clinical interview for DSM-IV-TR, non-patient edition; SDQ, sleep disturbance questionnaire; YMRS, Young mania rating scale.

polysomnography-measured SE, TST, % REM sleep and % stage 3 sleep, compared with healthy controls matched for age, gender, ethnicity, parental report of attention-deficit and hyperactivity disorder (ADHD) diagnosis, psychotropic medication usage and apnea–hypopnea index. In addition, according to their parents, children with bipolar disorder exhibited more nightmares, difficulty initiating sleep and morning headaches than matched controls. However, there was no significant between-group difference in polysomnography-measured SOL, REM latency, % stage 1, 2 and 4 sleep and NWAK.

Mullin et al. [32] reported that adolescents with bipolar disorder had significantly longer actigraphy-assessed TST but shorter WASO, compared with adolescents with ADHD combined type and healthy controls. The bipolar group also had significantly greater sleep diary-assessed NWAK than the ADHD group, but no difference as compared to healthy controls. There was no significant difference between the three groups in SE, SOL, sleep onset time, wake time and variability of TST, sleep onset time and wake time, as measured by actigraphy and sleep diary.

Comparison between at-risk and control participants

Actigraphy

Compared with controls, people at risk for bipolar disorder had significantly lower relative amplitude of the sleep–wake cycle (SMD = −0.43, 95% CI −0.83 to −0.02, I^2 = 43%) and variability in SE (SMD = 0.38, 95% CI 0.07 to 0.70, I^2 = 8%), but there was no significant difference in other sleep–wake parameters, including TST (SMD = −0.14, 95% CI −0.68 to 0.40, I^2 = 72%), SOL (SMD = −0.24, 95% CI −0.61 to 0.12, I^2 = 38%), WASO (SMD = −0.09, 95% CI −0.41 to 0.22, I^2 = 0%), SE (SMD = 0.02, 95% CI −0.26 to 0.30, I^2 = 0%), variability in TST (SMD = 0.29, 95% CI −0.01 to 0.60, I^2 = 0%), SOL (SMD = −0.12, 95% CI −0.57 to 0.33, I^2 = 54%), WASO (SMD = 0.33, 95% CI −0.02 to 0.69, I^2 = 0%) and interdaily stability (SMD = −0.25, 95% CI −0.55 to 0.05, I^2 = 0%) and intradaily variability (SMD = −0.10, 95% CI −0.56 to 0.37, I^2 = 57%) (Fig. S5). Ankers and Jones [14] reported no significant between-group difference in variability in WASO. Ritter et al. [7] reported no significant difference in TIB.

Sleep diary

Meyer and Maier [15] reported that participants at risk for bipolar disorder had significantly greater variability in TST relative to controls, but there was no significant difference in TST. Ankers and Jones [14] reported that high-risk individuals had later and more variable bedtimes relative to controls.

Questionnaire

Jones et al. [33] reported no significant between-group difference in PSQI scores.

Table 2
Key results of the included studies.

Study	Key results on sleep–wake disturbance
Ankers and Jones, 2009 [14]	HR significantly higher than MC in variability in actigraphy-derived TST and SE but lower in TST and relative amplitude. HR significantly later and more variable bedtimes. No significant difference in SOL, SE, SF, WASO, interdaily stability, intradaily variability and variability in SOL, SF and WASO.
Bullock and Murray, 2013 [65]	HR significantly lower than MC in actigraphy-derived relative amplitude. No significant difference in SOL, SE, TST, interdaily stability and intradaily variability.
Eidelman et al., 2010 [27]	BD significantly higher than HC in REM density. No significant difference between BD and HC in REM latency, % REM, 1st REM duration, % stage 1, % stage 2 and % SWS, as measured by PSG.
Eidelman et al., 2012 [66]	No significant difference between BD and HC in bedtime and wake time, as measured by sleep diary.
Gershon et al., 2012 [10]	BD significantly higher than HC in ISI, PSQI, sleep diary-derived TWT, actigraphy-derived TIB and variability in sleep diary-derived TWT and SE. No significant difference between BD and HC in other sleep indices, as measured by sleep diary and actigraphy.
Harvey et al., 2005 [5]	BD significantly higher than HC in PSQI score, actigraphy-derived TST and sleep diary-derived SOL. BD significantly higher than INS in actigraphy-derived TST. No significant difference between BD, HC and INS in other sleep indices, as measured by sleep diary and actigraphy.
Jones et al., 2005 [9]	BD significantly lower than HC in total activity counts but higher in interdaily stability and intradaily variability. No significant difference between BD and HC in TST, SOL, SE, SF, WASO, relative amplitude and variability in TST, SOL, SE, SF and WASO, as measured by actigraphy.
Jones et al., 2006 [33]	HR significantly lower than MC in SOL and variability in SF, as measured by actigraphy. No differences in TST, SE, SF, intradaily variability, interdaily stability, relative amplitude and variability in SOL, TST and SE.
Kaplan et al., 2012 [26]	No significant difference between BD and HC in SOL, WASO, TST, SE and NWAK, as measured by sleep diary and actigraphy.
Knowles et al., 1986 [29]	BD significantly higher than HC in shifts to stage 1, awake and movement time. No significant difference between BD and HC in SOL, WASO, TST, SE, % stage 1, % stage 2, % stage 3, % stage 4, % REM, REM latency, REM profusion, as measured by PSG.
Mehl et al., 2006 [31]	BD significantly lower than MC in SE, % REM and time in REM, but higher in time in stage 3, as measured by PSG. BD significantly worse than MC in severity of nightmare, difficulty initiating sleep and morning headache, as measured by sleep questionnaire. No significant difference between BD and MC in SOL, REM onset latency, time in stage 1, time in stage 2, time in stage 4 and NWAK, as measured by PSG.
Meyer and Maier, 2006 [15]	HR significantly higher variability in TST. No significant difference in TST.
Millar et al., 2004 [11]	BD significantly higher than HC in sleep diary-derived TST and SOL, actigraphy-derived TST, SOL and SE and variability in sleep diary-derived TST and WASO. No significant difference between BD and HC in other sleep indices, as measured by sleep diary and actigraphy.
Mullin et al., 2011 [32]	BD significantly higher than HC and ADHD-C in TST, but lower in WASO, as measured by actigraphy. BD significantly higher than ADHD-C in sleep diary-derived NWAK. No significant difference between BD, HC and ADHD-C in other sleep indices, as measured by sleep diary and actigraphy.
Ritter et al., 2012 [7]	BD significantly higher than HC in actigraphy-derived TST and SOL. No significant difference between BD, HC and at-risk group in SE, SF, WASO and variability in TST, SOL, SE, WASO and SF, as measured by actigraphy.
Rocha et al., 2013 [67]	BD significantly higher than HC in PSQI scores.
Salvatore et al., 2008 [8]	BD significantly higher than HC in TST, but lower in activity count, nocturnal activity % and daytime activity % and earlier in acrophase, as measured by actigraphy. No significant difference between BD and HC in amplitude and % daytime sleep, as measured by actigraphy.
Sitaram et al., 1982 [28]	BD significantly higher than HC in % REM and REM density in the 1st REM period, as measured by PSG. No significant difference between BD and HC in SOL, WASO, TST, SE, % SWS, REM latency and other sleep indices, as measured by PSG.
St-Amand et al., 2009 [12]	BD significantly higher than HC in ISI, ESS, sleep diary-derived "feeling exhausted upon awakening" and number of naps, but lower in actigraphy-derived activity counts. BD significantly higher than INS in actigraphy-derived SE and sleep diary-derived TST, SE and number of naps, but lower in sleep diary-derived SOL and WASO. No significant difference between BD, HC and INS in other sleep indices, as measured by actigraphy and sleep diary.
Talbot et al., 2012 [30]	BD significantly worse than HC in sleep diary-derived SOL, WASO, NWAK, TWT and SE. BD significantly lower than INS in sleep diary-derived SOL and WASO. No significant difference between BD, HC and INS in TIB, TST, bedtime, wake time, final arising time and terminal wakefulness, as measured by sleep diary.
Walz et al., 2012 [68]	BD significantly higher than HC in ESS and PSQI scores.

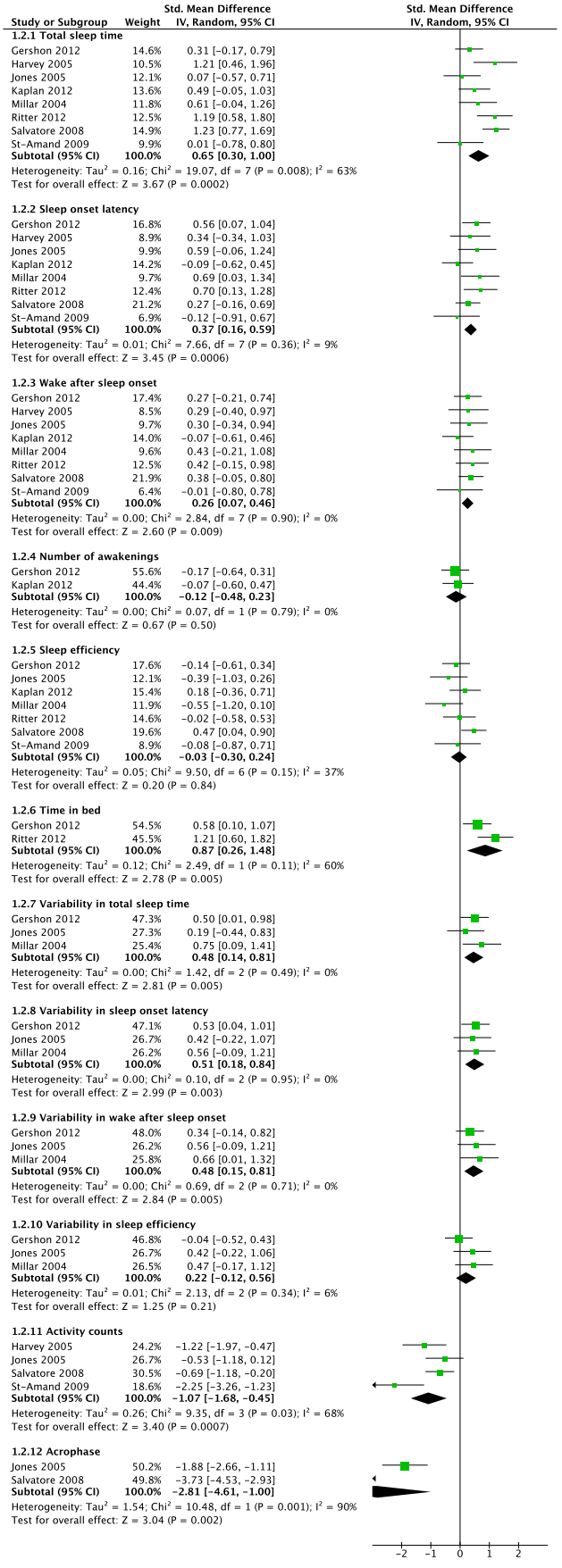
ADHD-C, attention-deficit and hyperactivity disorder-combined type; ESS, Epworth sleepiness scale; HC, healthy controls; HR, high-risk individuals; INS, primary insomnia; ISI, insomnia severity index; MC, matched controls; NWAK, number of awakenings; PSG, polysomnography; PSQI, Pittsburgh sleep quality index; REM, rapid-eye movement; SE, sleep efficiency; SF, sleep fragmentation; SOL, sleep onset latency; SWS, slow-wave sleep; TIB, time in bed; TST, total sleep time; TWT, total wake time; WASO, wake after sleep onset.

Discussion

The current paper provides the first systematic review and meta-analysis of sleep–wake disturbance in people with interepisode bipolar disorder and high-risk individuals. As studies in the field typically have small sample sizes, this review provides more precise estimates of the differences between patients and controls. We pooled together 531 people with interepisode bipolar disorder and 157 high-risk individuals *v.* 678 healthy controls and 67 people with primary insomnia. Our data suggest that adults with interepisode bipolar disorder appear worse than healthy controls in most sleep–wake variables and comparable to adults with primary insomnia in certain aspects. Sleep–wake disturbance in adults with interepisode bipolar disorder could be categorized into three major types: insomnia, hypersomnia and variability in sleep–wake patterns. Due to the limited data on children and adolescents with bipolar disorder and high-risk individuals, drawing a clear conclusion on sleep–wake disturbance in the two populations is not possible.

Sleep–wake disturbance in adults with interepisode bipolar disorder

In terms of insomnia, compared with healthy controls, adults with interepisode bipolar disorder were found to take longer to fall asleep and spend more time awake according to both sleep diary and actigraphy, have more awakenings during the night and lower sleep efficiency according to sleep diary, and have more severe insomnia symptoms and worse sleep quality according to questionnaire. Relative to adults with primary insomnia, adults with interepisode bipolar disorder spent a similar amount of time trying to fall asleep according to both sleep diary and actigraphy and to



stay awake during the night according to actigraphy, but they slept longer and had better SE according to both sleep diary and actigraphy. According to questionnaire, the bipolar group exhibited better sleep quality and endorsed fewer insomnia symptoms compared with the primary insomnia group.

In terms of hypersomnia, compared with healthy controls, adults with interepisode bipolar disorder spend longer time in bed according to both sleep diary and actigraphy, have lower activity counts and sleep longer according to actigraphy and have more severe daytime sleepiness according to questionnaire.

In terms of variability in the sleep–wake cycle, adults with interepisode bipolar disorder had greater variability in TST, SOL and WASO according to both sleep diary and actigraphy and greater variability in SE according to sleep diary. They also had more unstable interdaily and intradaily rest-activity cycles according to actigraphy.

There was some evidence that the circadian sleep–wake cycle of adults with interepisode bipolar disorder is advanced, as indicated by earlier acrophase, based on our meta-analysis of two actigraphic studies [8,9]. However, both REM latency and duration of the first REM period did not differ between patients with interepisode bipolar disorder and healthy controls. It is also inconsistent with the finding of delayed circadian rhythm of melatonin secretion in interepisode bipolar disorder [34]. In view of the small number of studies available and the short period of observation in the previous studies, no definite conclusions can be made on the phase position of the sleep–wake cycle in interepisode bipolar disorder.

Other than higher % stage 1, there were no significant between-group differences in any of the polysomnography-measured variables.

Sleep–wake disturbance in children and adolescents with interepisode bipolar disorder

To our knowledge, only two studies have been published on the sleep of children and adolescents with interepisode bipolar disorder. The data suggest that children with bipolar disorder also have impaired sleep according to polysomnography, when compared with matched controls. The adolescent study, nevertheless, found that adolescents with interepisode bipolar disorder slept better than controls objectively according to actigraphy and yet had difficulty maintaining sleep subjectively based on sleep diary.

Sleep–wake disturbance in high-risk individuals

Based on our meta-analysis, people with an elevated risk of developing bipolar disorder have weak and more unstable rest-activity cycles, as indicated by lower relative amplitude, and higher variability in SE in comparison with controls. High-risk individuals also have greater variability in TST relative to controls when the variable was measured with sleep diary according to one study [15], but our meta-analysis suggests that the difference was marginally insignificant ($P = 0.06$) when measured with actigraphy. There was no other significant difference in sleep–wake parameters between high-risk individuals and healthy controls.

Discrepancies between subjective and objective sleep–wake variables

Our data suggest that there might be discrepancies between subjective and objective sleep–wake variables in adults with

Fig. 2. Adults with interepisode bipolar disorder vs. healthy controls on actigraphy-derived variables. Std. Mean Difference, standardized mean difference; IV, inverse variance; Random, random effects model; CI, confidence interval; Tau^2, between-study variance; Chi^2, within-domain heterogeneity; df, degree of freedom; P, p value; I^2, percentage of the variability in effect estimates due to heterogeneity.

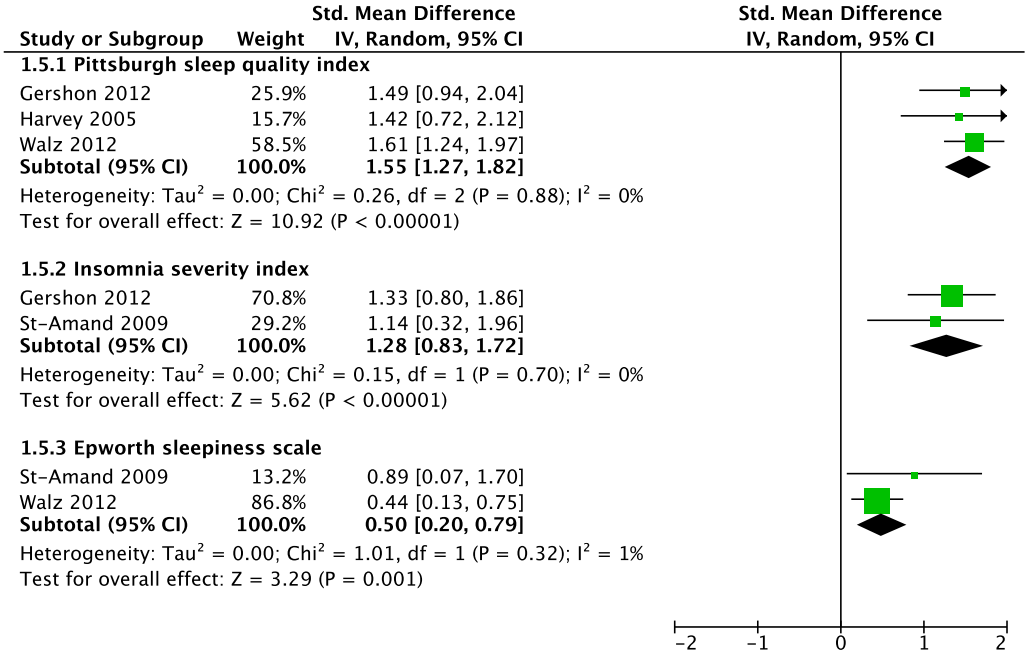


Fig. 3. Adults with interepisode bipolar disorder vs. healthy controls on questionnaire-derived variables. Std. Mean Difference, standardized mean difference; IV, inverse variance; Random, random effects model; CI, confidence interval; Tau^2, between-study variance; Chi^2, within-domain heterogeneity; df, degree of freedom; P, *p* value; I^2, percentage of the variability in effect estimates due to heterogeneity.

interepisode bipolar disorder. In the meta-analysis, there was only one significant difference out of ten polysomnography-derived variables between adults with interepisode bipolar disorder and healthy controls, while we found nine significant differences out of 12 variables in both sleep diary and actigraphy comparisons among the two groups. A recent study reported moderate to high concordance between actigraphy and polysomnography variables in interepisode bipolar disorder, with Pearson's correlations ranging from 0.33 to 0.92 [26]. Hence, the null findings of the polysomnography analyses could be due to several methodological limitations. First, the analyses on polysomnography data might lack statistical power to detect significant differences, as they were based on only three studies. Second, the polysomnography studies had short assessment periods (mostly one to two nights). It has been argued that seven nights of polysomnography recordings need to be averaged to achieve adequate stability in estimating sleep variables and sensitive detection of significant differences [35]. Finally, all the polysomnography studies were conducted in laboratory settings, which might facilitate sleep by obviating the usual environmental stimuli that perpetuate sleep disturbance [36].

Nevertheless, it is important to note that discrepancies between subjective and objective sleep–wake variables are the norm rather than the exception. In their review, Harvey and Tang [37] critically examined the robust finding in the insomnia literature that people with insomnia exhibit a tendency to overestimate SOL and underestimate TST. They evaluated thirteen reasons that could account for this finding, such as worry and a tendency to perceive sleep as wakefulness. Therefore, there may be reasons other than methodological issues that are responsible for the discrepancies.

The effects of medications on sleep–wake patterns in interepisode bipolar disorder

Psychotropic medications often affect sleep (for a review, see [38,39]). For example, lithium has been shown to improve nighttime sleep and increase daytime sleepiness at least in the short term [40], as well as increase SWS and REM latency and decrease REM sleep in healthy and depressed individuals [41]. However, very few studies have been conducted to examine the effects of medications on sleep–wake patterns in interepisode bipolar disorder. It is difficult to undertake such studies due to ethical and pragmatic concerns. Therefore, randomized controlled trials of maintenance pharmacological treatments for patients with interepisode bipolar disorder provide valuable insights into the effects of medications on sleep–wake patterns in the population. For example, several clinical trials reported that hypersomnia was significantly greater with atypical antipsychotics (e.g., olanzapine and quetiapine) than with placebo in interepisode bipolar disorder, whereas insomnia was greater with placebo than with atypical antipsychotics [42–44]. A pooled analysis of two clinical trials reported that lithium had significantly higher rates of hypersomnia than placebo and lamotrigine in interepisode bipolar disorder [45]. However, while these data provide valuable information about the effect of a medication on sleep–wake patterns in interepisode bipolar disorder, it is difficult to determine the joint effects of multiple medications on sleep–wake patterns. In addition, some may argue that the samples are unrepresentative of the bipolar population, as people with bipolar disorder often receive polypharmacy [46].

Several authors have attempted to tackle the complex methodological confound of medication effects. For instance, Eidelman et al. [47] categorized medications according to their effects on REM, SWS, and/or stage 2 sleep. They found that adults with interepisode bipolar disorder who took a REM-suppressing drug (e.g., fluoxetine) had longer REM latency than those who took a drug with no effect or an enhancing effect on REM (e.g., bupropion). Those who took a REM-enhancing drug also had greater REM density than those who took a medication with no effect on REM. However, % stage 2 and % SWS were not affected by medications.

Kaplan et al. [48] calculated medication load scores that took into account differences in medication classes and dosage to examine the confounding effects of medications on hypersomnia in interepisode bipolar disorder. They found no differences in medication classes, number of medications taken, and medication load

scores between those who did and did not experience hypersomnia. Taken together, by adopting novel analytical approaches, we might be able to conduct studies of sleep–wake patterns in interepisode bipolar disorder that uphold scientific rigor and reflect clinical reality.

Insomnia in interepisode bipolar disorder and its implications

Our meta-analysis suggests that adults with bipolar disorder appear to also have insomnia symptoms, even when they are between episodes. Low nocturnal level of melatonin [49], hypersensitivity of the melatonin suppression effects of light [34,50] and hypercortisolemia [51,52] in interepisode bipolar disorder may contribute to the insomnia symptoms. Cognitive elements may also explain the insomnia symptoms reported by patients with bipolar disorder. Harvey et al. [5] found that holding more dysfunctional beliefs and attitudes about sleep was robustly associated with more severe sleep disturbance among individuals with bipolar disorder. In the past few years, there has been a growing interest in adopting cognitive behavioral therapy for insomnia (cognitive behavioral therapy for insomnia (CBT-I)) in interepisode bipolar disorder [4,22]. Nevertheless, sleep restriction and stimulus control, two core components of CBT-I, have been argued to be contraindicated for interepisode bipolar disorder because sleep deprivation may trigger manic episodes in some people with bipolar disorder. Encouragingly, a recent study suggests that CBT-I with controlled sleep restriction may be a safe and efficacious treatment for insomnia in interepisode bipolar disorder [53].

Hypersomnia in interepisode bipolar disorder and its implications

Both adults and adolescents with interepisode bipolar disorder were found to have longer sleep duration relative to healthy controls. Adults with interepisode bipolar disorder also spent more time in bed and experienced more severe daytime sleepiness and lower activity counts. Previous studies have suggested that hypersomnia may play a unique role in bipolar disorder. Kaplan et al. [48] showed that complaints of hypersomnia were found in 25% of the sample and were associated with depressive symptoms six months later. It has also been found that hypersomnia can differentiate bipolar II disorder from major depressive disorder, with a positive predictive value of around 70% [54,55]. While hypersomnia in interepisode bipolar disorder might be caused by circadian rhythm disruption, it can also be due to psychological processes, such as lack of motivation and interest [56–59]. Researchers have raised the possibility of utilizing cognitive-behavioral, pharmacological and light therapies for hypersomnia in bipolar disorder [60]. It should be emphasized, nevertheless, that empirical data have yet to be produced to validate these treatments.

Variability in the sleep–wake cycle in interepisode bipolar disorder and its implications

Our findings suggest that both adults with interepisode bipolar disorder and people at risk for bipolar disorder have more unstable sleep–wake patterns relative to controls. The findings support the instability model of bipolar disorder proposed by Goodwin and Jamison [61] and the focus on regularizing sleep–wake schedules as psychosocial interventions for bipolar disorder. There is also evidence that simply setting regular bedtimes and rise times could give rise to an improvement in sleep in many people with bipolar disorder [53]. As variability in the sleep–wake cycle is found in adults with interepisode bipolar disorder and people at risk for bipolar disorder, this phenomenon might be considered as a possible endophenotype for bipolar disorder. However, it is uncertain whether sleep–wake variability is an independent phenomenon or a result of chronic insomnia, as night-to-night sleep variability is also common in people with chronic insomnia [62,63]. There is also limited neurophysiological evidence to support the circadian instability model in bipolar disorder [20].

Limitations and future directions

The findings of the current systematic review and meta-analysis should be interpreted with caution. First, some meta-analytic comparisons of sleep–wake variables included a limited number of studies. Second, high heterogeneity was found in several variables, with I^2 above 75%. The high heterogeneity may be due to the small number of studies available. Third, the criteria for the interepisode state differ across studies. Future research should employ symptom severity interviews with stringent cut-offs to control for the impact of subsyndromal mood symptoms on sleep. Fourth, the reviewed studies did not control for comorbid anxiety disorders, which might contribute to sleep–wake disturbance in interepisode bipolar disorder. Future studies could consider comparing the sleep of interepisode bipolar disorder with and without anxiety comorbidity or controlling for anxiety symptoms.

Fifth, the samples of most included studies often were not medication-free, although samples including only unmedicated patients with bipolar disorder would be unethical and unrepresentative. As many of the psychotropic medications used in bipolar disorder are sedative, this limitation is unlikely to account for the insomnia symptoms and the variability in sleep–wake patterns in people with interepisode bipolar disorder. Nevertheless, medications may also have caused excessive daytime sleepiness, accounting for the hypersomnia findings. Future studies should adopt and refine methodological and analytical approaches that reduce the confounding effects of medications, such as those proposed by Eidelman et al. [47] and Kaplan et al. [48]. Studies that include adequate controls, such as matched healthy controls and non-bipolar patients with matched psychotropic medication usage, to investigate short-term, intermediate-term and long-term effects of medications on sleep–wake patterns are warranted. Also, future randomized controlled trials of maintenance pharmacotherapies in interepisode bipolar disorder should include measures of sleep–wake patterns, such as sleep diary, actigraphy, and polysomnography, as secondary outcome measures. In addition, we recommend that future studies report the name, dosage, and duration of use for all major psychotropic medications taken by patients with bipolar disorder and examine if they have associations with sleep–wake parameters [26,64].

Finally, concerning actigraphy studies, differences in algorithms for scoring and detecting wake threshold might contribute to the differences in findings. Future actigraphy studies should report what actigraphs and algorithms they use. There is also a need for standardization in algorithms to allow for more precise comparisons between studies. As a first step, Kaplan et al. [26] reported that the medium wake-threshold setting (40 counts/min) for Actiwatch AW-64 yielded the highest concordance of actigraphy with polysomnography and sleep diary data in adults with interepisode bipolar disorder.

The findings of the current study show that adults with bipolar disorder, outside of acute mood episodes, exhibit three major clusters of sleep–wake pathology – insomnia, hypersomnia and variability in the sleep–wake pattern. Daily 24-h monitoring of the rest-activity pattern over an extended period is required to delineate the instability of the circadian rhythm in interepisode bipolar disorder. There is also a pressing need for research on the impact of interventions on sleep–wake disturbance in interepisode bipolar disorder. The current systematic review and meta-analysis

represents an important first step toward developing a more fine-tuned understanding of sleep–wake disturbance in interepisode bipolar disorder, with the possibility of finding candidate endophenotypes for bipolar disorder and providing a foundation for the development of novel interventions targeted to improve sleep–wake patterns in people with interepisode bipolar disorder.

Practice points

1) People with bipolar disorder are worse than healthy controls in most sleep–wake variables and comparable to people with primary insomnia in certain aspects, even when they are not in a mood episode.
2) The sleep–wake profile of adults with interepisode bipolar disorder shows an increase in sleep onset latency, wake after sleep onset, time in bed, and night-to-night variability in total sleep time, sleep onset latency, and wake after sleep onset according to both sleep diary and actigraphy and an increase in subjective insomnia symptoms and daytime sleepiness, as well as a reduction in subjective sleep quality according to questionnaire.
3) Variability in the sleep–wake cycle, which is found in both people with interepisode bipolar disorder and high-risk individuals, could be considered as a candidate endophenotype for bipolar disorder.

Research agenda

Future studies should:

1) Employ familial high-risk samples to evaluate the role of variability in the sleep–wake cycle in the onset, course, and outcome of bipolar disorder.
2) Adopt symptom severity interviews with stringent cut-offs to control for the impact of subsyndromal mood symptoms on sleep.
3) Compare the sleep of interepisode bipolar disorder with and without anxiety comorbidity or control for anxiety symptoms.
4) Adopt and refine methodological and analytical approaches that reduce the confounding effects of medications.
5) Include adequate controls, such as matched healthy controls and non-bipolar patients with matched psychotropic medication usage, to investigate short-term, intermediate-term and long-term effects of medications on sleep–wake patterns.
6) Report the name, dosage, and duration of use for all major psychotropic medications taken by patients with bipolar disorder and examine if they have associations with sleep–wake parameters.
7) Report what actigraphs are used. We need to standardize algorithms to allow for more precise comparisons between studies.
8) Develop novel treatments for sleep–wake disturbance in interepisode bipolar disorder targeting insomnia, hypersomnia and variability in the sleep–wake cycle.

Declaration of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2014.06.006.

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